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Original Article

Retrospective Analysis of Clopidogrel Resistance Tests

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Abstract

Background: Clopidogrel binds to P2Y12 and inhibits platelet aggregation. Clopidogrel resistance can be categorized into two main categories: laboratory clopidogrel resistance and clinical clopidogrel resistance. Laboratory clopidogrel resistance refers to the inadequate in vitro antiplatelet effects of clopidogrel. In the present study, we aimed to evaluate the clopidogrel resistance test results from the perspective of laboratory specialists.

Methods: All clopidogrel resistance test results from the Bilkent City Hospital laboratory information system, between February 1, 2019, and May 31, 2025, were collected. Clopidogrel resistance tests were performed using the adenosine diphosphate-induced platelet aggregation method using an aggreometer device (Stago Chrono-Log Model 700). Data were expressed as mean, minimum, and maximum levels, numerically and as percentages. The Chi-square test was performed a categorical data comparison between the created groups. IBM SPSS Statistics performed statistical analyses for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA).

Results: A total of 285 clopidogrel resistance test results were included. Negative and positive clopidogrel test results were as follows: 95 (33.3 %) and 190 (66.7 %). The present study consisted of 98 (34.4 %) females, 187 (65.6 %) males' clopidogrel resistance tests. There were 107 (37.5%) clopidogrel resistance test results in the under 65 years old group, while there were 178 (62.5%) in the 65 and older years group. The neurology clinic requested clopidogrel resistance tests mostly (N:72, 62.5 %). No statistical differences were found in gender among age intervals ($p>0.05$), in clopidogrel resistance tests among gender ($p>0.05$), and in clopidogrel resistance tests among age intervals ($p>0.05$).

Conclusion: The most appropriate laboratory test to assess clopidogrel resistance has not yet been determined. The present study, evaluated from a laboratory perspective, may be useful for future research; however, prospective studies combining laboratory and clinical findings may be more effective.

Keywords: Platelet Aggregation, Thrombosis, Blood Coagulation

INTRODUCTION

The formation of a blood clot within a blood vessel is thrombosis (1). Normal hemostasis involves sensitive interactions between the coagulation and fibrinolytic systems. Deviations in the normal hemostasis/blood clotting system cause thrombosis (2). Thrombosis occurs through three basic steps: platelet adhesion, platelet activation, and platelet aggregation (3). In platelet adhesion, interactions occur between the GP Ib/V/IX receptor complex located on the surface of platelets and the collagen and von Willebrand factor (vWF) and its receptor when exposed to the site of vascular injury (1).

Adenosine diphosphate (ADP) interacts with the platelet membrane ADP receptor (P2Y12), which is involved in ADP-induced activation of the glycoprotein IIb/IIIa receptor. Activation of the glycoprotein IIb/IIIa receptor leads to increased platelet degranulation and thromboxane production, as well as prolonged platelet aggregation (4).

Blocking P2Y12 is a potent pharmacological antiplatelet strategy for the treatment of arterial thrombosis caused

by coronary atherosclerosis and the prevention of thrombosis. Platelet adhesion, activation, and aggregation are important in atherothrombosis. Intracoronary atherothrombosis is one of the most common causes of acute coronary syndrome; it plays a role in complications associated with percutaneous coronary intervention, including recurrent acute coronary syndrome, procedure-related myocardial infarction, or stent thrombosis (5,6).

Clopidogrel binds to P2Y12 and inhibits platelet aggregation (7). Clopidogrel, the P2Y12 inhibitor, is a second-generation thienopyridine (8). Clopidogrel is a prodrug and does not have a direct effect on antiplatelet activity. The antiplatelet effect occurs through oxidation of the active clopidogrel metabolite by cytochrome P450 enzymes. After oral administration, the drug is absorbed with approximately 50% bioavailability (9). The highest level of platelet inhibition due to clopidogrel occurs within 2 to 5 hours after a single dose of 400 mg. The same level of inhibition is achieved after 3 to 7 days with daily use of 75 mg of clopidogrel (10). Clopidogrel has a role in reducing fibrinogen levels, and it also inhibits erythrocyte aggregation (11,12). Clopidogrel, which has been widely used in recent years, has bleeding and hematological complications, but considering its hematological side effects, it is still one of the safest drugs in the thienopyridine class (13).

Clopidogrel and aspirin inhibit platelet aggregation through different pathways. Combining antiplatelet therapy offers additional and complementary benefits compared with either drug alone (14,15). The CAPRIE study, conducted in a selected patient population, demonstrated significant benefits of clopidogrel therapy compared with aspirin alone (16). The combined use of clopidogrel and aspirin is the gold standard for reducing platelet activation and aggregation in patients with acute coronary syndromes and those undergoing stent placement (14,15).

However, despite dual antiplatelet therapy, recurrent ischemic events are common in patients with acute coronary syndromes and those undergoing percutaneous coronary intervention. Stent thrombosis, in particular, can have serious consequences. The antiplatelet activity of clopidogrel varies among individuals (17). Some individuals experience recurring cardiovascular events despite the use of potent antiplatelet drugs such as aspirin and clopidogrel. This has led to the emergence of the concept of unresponsiveness or resistance to antiplatelet drugs (18). Gruber et al. stated that the definition of unresponsiveness or resistance to an antiplatelet drug is the failure of the antiplatelet drug to inhibit its target of action (15).

Clopidogrel resistance can be categorized into two main categories: laboratory clopidogrel resistance and clinical clopidogrel resistance. Laboratory clopidogrel resistance refers to the inadequate in vitro antiplatelet effects of clopidogrel. Clinical clopidogrel resistance refers to treatment failure, and patients experience cardiovascular events despite clopidogrel use (19). Laboratory and clinical resistance are not the same. Not every patient with laboratory resistance will experience a cardiovascular event. Clinical resistance is associated with inadequate treatment. Laboratory resistance does not occur in every patient receiving antiplatelet drug therapy. Sometimes, laboratory and clinical clopidogrel resistance coexist (20).

In the present study, we aimed to evaluate clopidogrel resistance test results retrospectively from the perspective of laboratory specialists and share the data with the existing literature.

METHODS

Study Design and Data Collection

The research was conducted at Bilkent City Hospital. Clopidogrel resistance test results recorded in the hospital's laboratory information system between February 1, 2019, and May 31, 2025, were retrospectively reviewed. For each patient, only the first available test result was included in the analysis to avoid duplication and ensure data consistency

Laboratory Analysis

Clopidogrel resistance testing was performed in an external reference laboratory contracted with Bilkent City Hospital. The analysis was based on adenosine diphosphate (ADP)–induced platelet aggregation, measured using an aggregometer device (Stago Chrono-Log Model 700).

Ethical Approval

This study received ethical approval from the Ethics Committee of Bilkent City Hospital (Approval No: TABED 2-25-1352; Date: June 25, 2025).

STATISTICAL ANALYSIS

Continuous variables were summarized as mean, minimum, and maximum values, whereas categorical variables were expressed as frequencies and percentages. Differences between categorical variables across the study groups were assessed using the Chi-square test. A p-value < 0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Study Population

A total of 285 clopidogrel resistance test results were included in the final analysis. Study groups were stratified according to gender, age, and clopidogrel resistance test results.

Table 1. Distribution of Clopidogrel Resistance Test Results by Demographic and Clinical Characteristics

Variable	N	%
Female	98	34.4
Male	187	65.6
Under 65 years	107	37.5
65 years and older	178	62.5
Clopidogrel Resistance Test Results		
Negative	95	33.3
Positive	190	66.7
Requesting Clinics		
Neurology	178	62.5
Neurosonology	79	27.7
Neurosurgery	9	3.2
Rehabilitation	5	1.8
Cardiovascular Surgery	4	1.4
Cardiology	3	1.1
Infectious Diseases	1	0.4
Interventional Radiology	1	0.4
Chest Diseases	1	0.4
Internal Diseases	1	0.4
Nephrology	1	0.4
Neuromuscular Diseases	1	0.4
Organ Transplantation Intensive Care	1	0.4

Gender Distribution

Among all participants, 98 (34.4%) were female and 187 (65.6%) were male. The Neurology Clinic accounted for the majority of clopidogrel resistance test requests (n = 72; 62.5%) (Table 1).

Age Distribution

The mean age of participants younger than 65 years was 56.2 years (range: 37–64), while the mean age in the ≥65 years group was 73.9 years (range: 65–92). There were 107 (37.5%) test results in individuals under 65 years and 178 (62.5%) in those aged 65 years or older.

Clopidogrel Resistance Results

Overall, 95 (33.3%) of the tests were negative, while 190 (66.7%) were positive for clopidogrel resistance. The distribution of clopidogrel resistance across subgroups is detailed in the following comparisons.

Comparative Analyses

Gender and Age: The gender distribution across age intervals is summarized in Table 2 (p = 0.559).

Clopidogrel Resistance and Gender: The relationship between clopidogrel resistance and gender is presented in Table 3 and Figure 1 (p = 0.659).

Clopidogrel Resistance and Age: The comparison of clopidogrel resistance across age intervals is shown in Table 4 and Figure 2 (p = 0.484).

DISCUSSION

Antiplatelet drugs play a pivotal role in reducing the risk of thromboembolic events, particularly in patients with cerebrovascular diseases or those undergoing neurovascular stent placement (21). By inhibiting platelet aggregation, these agents aim to prevent ischemic complications. However, in a subset of patients, the expected therapeutic response is not achieved, a condition first described in the 1980s and referred to as antiplatelet therapy resistance (22). Among the commonly used agents, clopidogrel resistance has been associated with recurrent ischemic events, particularly in high-risk populations (20).

Reported prevalence rates of clopidogrel resistance

Table 2. Gender Distribution Among Age Intervals

Age Interval	Female n (%)	Male n (%)	p value*
<65 years	37 (34.6)	70 (65.4)	0.559
65 years and older	61 (34.3)	117 (65.7)	

Chi-square test was used for comparison.

Table 3. Clopidogrel Resistance Tests by Gender

Clopidogrel Resistance Status	Gender	n	%	p value*
Negative	Female	31	32.6	0.659
	Male	64	67.4	
Positive	Female	67	35.3	
	Male	123	64.7	

Table 4. Clopidogrel Resistance Tests by Age Intervals

Clopidogrel Resistance Status	Age Group	n	%	p*
Negative	Under 65 years	35	36.8	0.484
	65 years and older	60	63.2	
Positive	Under 65 years	72	37.9	
	65 years and older	118	62.1	

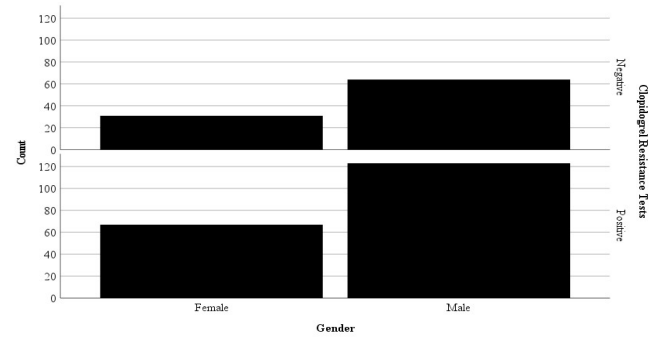

Figure 1. Clopidogrel Resistance Tests Among Genders

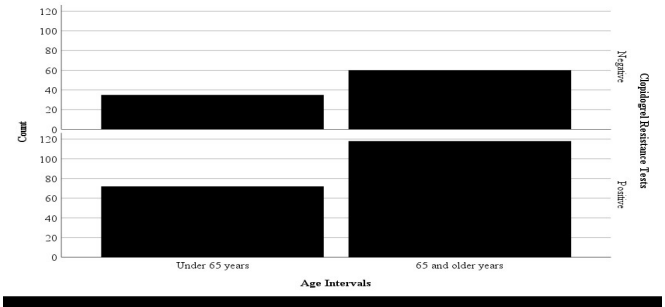

Figure 2. Clopidogrel Resistance Test Results Among Age Intervals

vary widely across studies. In a review by Nguyen et al., the prevalence was found to range between 4% and 30% (23). İyigündoğdu et al. reported a rate of 17.2% among patients followed for carotid artery stenting in neurology clinics (24). Similarly, a separate study involving patients with carotid stents documented a 19.0% resistance rate, while Müller-Schunk et al. reported 28% in patients with supra-aortic stents (25,26). In the present study, the prevalence of clopidogrel resistance was notably higher, at 66.7%. This discrepancy may be attributable to the inclusion of all laboratory clopidogrel resistance test data, independent of patients' underlying diagnoses or clinical settings. Such inclusion likely captures a broader patient spectrum, potentially inflating the observed rate compared with disease-specific cohorts.

Prabhakaran et al. identified a significant association between advancing age and reduced platelet inhibition, suggesting that diminished cytochrome P450 3A4 activity with age may impair clopidogrel metabolism and activation (27). However, other studies, including those by Ryu et al., Kim et al., and İyigündoğdu et al., found no significant age-related difference in clopidogrel responsiveness (21,24,28). Consistent with these findings, our study, which divided participants into two groups (<65 years and ≥65 years), demonstrated no statistically significant difference in clopidogrel resistance between the two age categories.

Previous investigations by Kim et al., Ryu et al., and Atasoy et al. similarly reported no significant gender differences in clopidogrel resistance (21,28,29). The present study supports these observations, finding no statistical difference between males and females. Nonetheless, some reports have suggested a higher prevalence of resistance among females, potentially reflecting pharmacokinetic and hormonal differences affecting clopidogrel absorption and metabolism (24,30). These conflicting results highlight the need for larger, well-controlled studies to clarify the influence of gender on clopidogrel response.

The mechanisms underlying clopidogrel resistance are multifactorial. Genetic polymorphisms affecting cytochrome P450 isoenzymes, reduced drug bioavailability, interindividual variability in baseline platelet reactivity, and accelerated platelet turnover have all been implicated (31). Although pre-procedural clopidogrel resistance testing may offer potential value in predicting thromboembolic risk, randomized controlled trials are still required to confirm its clinical utility and to define management strategies for resistant patients. Furthermore, the lack of standardized testing methods, including differences in agonists, assay platforms, and cutoff definitions, complicates cross-study comparisons. Despite the growing body of literature, a consensus on the clinical interpretation and management of clopidogrel resistance has yet to be reached (24).

The present study was conducted at Bilkent City Hospital, one of the largest tertiary healthcare centers in Türkiye, and utilized an extensive dataset comprising clopidogrel resistance test results collected between February 1, 2019, and May 31, 2025. The inclusion of a large sample size over a prolonged study period provides a robust overview of the real-world prevalence and demographic distribution of clopidogrel resistance. This comprehensive dataset strengthens the reliability of the observed patterns and enhances the generalizability of the findings within similar clinical settings.

Several limitations should be acknowledged. First, the retrospective design of the study restricted the ability to control for preanalytical factors that may influence clopidogrel resistance testing. Second, detailed clinical information regarding patients' concurrent medications, comorbidities, or treatment adherence was unavailable, which may have confounded the interpretation of resistance rates. Lastly, the data were analyzed primarily from a laboratory-based perspective, without incorporating direct clinical outcomes, which limits causal inferences regarding the association between laboratory resistance results and thromboembolic events.

CONCLUSION

Platelet function testing plays a crucial role in the management of cardiovascular and cerebrovascular diseases; however, the relationship between in vivo platelet activity and ex vivo laboratory test results remains uncertain [20]. At present, no single laboratory method has been universally accepted as the gold standard for assessing clopidogrel resistance (32). The present study, conducted from a laboratory-based perspective, provides valuable real-world insight into the prevalence and distribution of clopidogrel resistance. Nevertheless, prospective, multicenter studies that integrate laboratory findings with clinical outcomes are needed to better elucidate the mechanisms and clinical implications of clopidogrel resistance and to guide individualized antiplatelet therapy in the future.

DECLARATIONS

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Bilkent City Hospital, Ankara, Türkiye (Approval No: TABED 2-25-1352; Date: June 25, 2025). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the principles outlined in the Declaration of Helsinki.

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author, upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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